

FORM A

TO THE MINISTRY OF INDUSTRY, COMMERCE AND ARTISANSHIP
 ITALIAN PATENT AND TRADEMARK OFFICE - ROME

APPLICATION FOR PATENT FOR INDUSTRIAL INVENTION, RESERVE DEPOSIT, ANTICIPATED PUBLIC AVAILABILITY

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D. TITLE proposed class (sec/cl/subcl) group/subgroup

"A new apparatus capable of modulating the neurovegetative system and integrating its action with that of the central nervous system: applications in the therapy of the vascular system and orthopedic diseases"

ANTICIPATED PUBLIC AVAILABILITY NO

E. INVENTORS

- 1) Piccone Lorenzo 2)
 3) 4)

DOCUMENTATION INCLUDED

- Doc. 1) N. 2 copy of 18 pages of summary with main drawing, description and claims (1 copy compulsory)
- Doc. 2) N. 2 copy of 15 tables of drawings (1 copy compulsory if cited in the description)
- Doc. 3) N. 1 commissioning letter, ~~power of attorney or reference to General Power of attorney~~
- Doc. 4) 0 inventor's designation

8) Receipt for the payment a total of Lire Fivehundredsixtyfivethousand #compulsory

COMPILED 28/07/2000 SIGNATURE(S) OF THE APPLICANT(S): Banfi Paolo

CONTINUES YES/NO NO (signature)

IS AN AUTHENTICATED COPY REQUIRED YES/NO YES

PROVINCIAL OFFICE OF IND., COMM. AND ART. OF Milan code 15

CITATION OF DEPOSIT APPLICATION NO. MI2000A 001733

Year TWOTHOUSAND, day TWENTYEIGHT, month JULY

The above Applicant(s) has(have) presented the present application to me undersigned with No.00 additional sheets for the grant of the above indicated patent.

I. GENERAL NOTES OF THE ISSUING OFFICER

THE APPLICANT
 (signature)

THE ISSUING OFFICER
 M. CORTONESI (signature)

SUMMARY OF THE INVENTION WITH MAIN DRAWING, DESCRIPTION AND CLAIMS

APPLICATION NUMBER MI2000A001733

FILING DATE 28-07-2000

PATENT NUMBER

ISSUE DATE

D. TITLE

"A new apparatus capable of modulating the neurovegetative system and integrating its action with that of the central nervous system: applications in the therapy of the vascular system and orthopedic diseases"

L. ABSTRACT

It is described a new apparatus capable of modulating the neuro-vegetative system and integrating the neuro-vegetative action with that of the central nervous system. This method it is not invasive because it uses pulses transmitted through the skin; the intensity grade of the stimulus is controlled directly by the patient to reach a better integration with the central nervous system.

This invention is effective in treating the vascular affections consequent on obstruction of the arteries of the legs, heart and brain because it induces vasodilatation, increases the blood flow and the production of new vessels. This method is furthermore capable of improving lesions of the spinal column, in particular those that hit the back and the neck as well as other orthopedic pathologies.

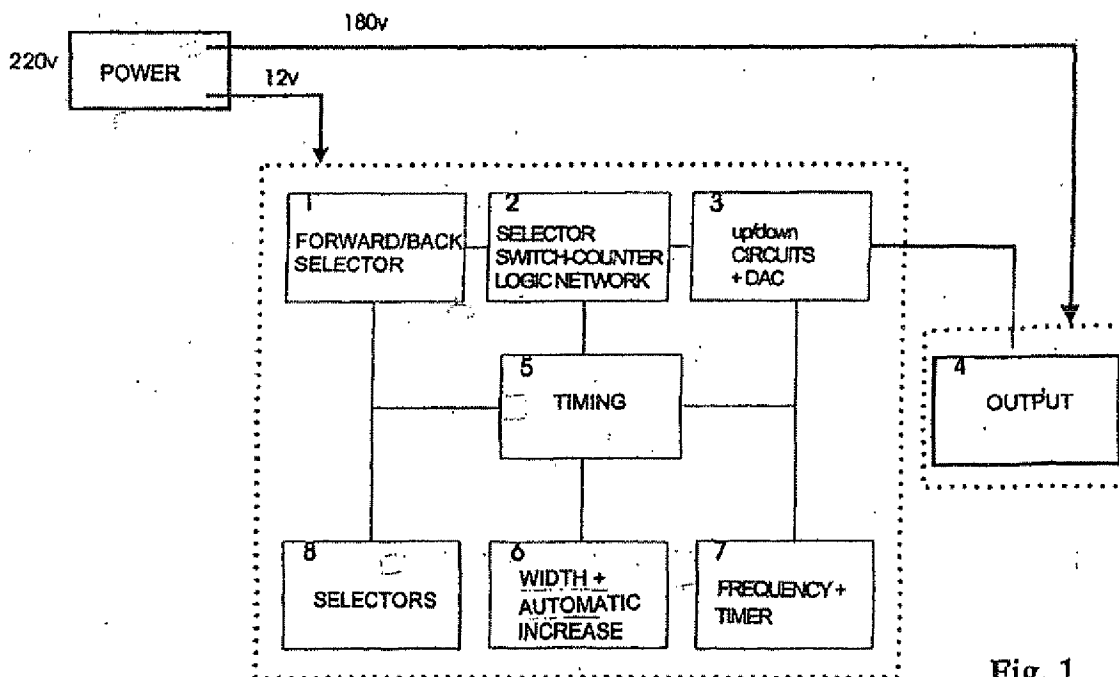
M. DRAWING

Fig. 1

Description of the patent for industrial invention having title:

"A NEW APPARATUS CAPABLE OF MODULATING THE NEUROVEGETATIVE SYSTEM AND INTEGRATING ITS ACTION WITH THAT OF THE CENTRAL NERVOUS SYSTEM: APPLICATIONS IN THE THERAPY OF THE VASCULAR SYSTEM AND ORTHOPEDIC DISEASES"

In the name of: PICCONE LORENZO

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* *

Purpose of invention

This invention provides for an apparatus and an innovative method suitable for regulating the function of the neurovegetative system integrating it with that of the central nervous system. This effect is achieved by administering electrical pulses to the skin level, the intensity of the pulses being controlled directly by the patient.

The new method is capable of inducing vasodilatation, stimulating neoangiogenesis and increasing blood flow. The regulation of the vascular flow obtained with this new technology allows to treat vascular diseases involving organic obstruction of the arteries, which often affect the lower limbs, heart and brain. The new technology also allows effective treatment of disorders of the rachis, especially the neck and the lumbosacral area.

The same apparatus might be effectively used also for the treatment of several other orthopaedic pathologies, involving inflammation and proprioceptive sensory alterations caused by imbalance of the muscular and vascular tone.

Basis of the invention

Atherosclerosis and thrombosis are frequent causes of arterial obstruction.

Atherosclerosis is responsible for most cases of arterial occlusion affecting the myocardium, brain and peripheral arteries.

Arterial obstruction or narrowing causes reduction in blood flow either during exercise or at rest. The clinical signs result from ischaemia. The atherosclerotic lesions which affect large and small blood vessels in diabetics are very similar to

those which appear in non-diabetics, however, they appear earlier, worsen more quickly and are more frequent in the case of diabetics. Distal arterial occlusion below the knee together with microvascular alterations and neurological lesions are responsible for gangrene. The symptoms are intermittent claudication and pain at rest caused by ischaemia. Diabetic foot, which is caused by a combination of vasculopathy, neuropathy and infection, is one of the most dangerous complications of diabetes, and is the cause of most amputations. Amputation of the foot or leg is five times as frequent in diabetics as in non-diabetics. Angina and myocardial infarction are the most frequent complications of occlusion or stenosis of the coronary artery.

These local actions, together with those of the autonomic nervous system and the vascular system, cause vasoconstriction when activated, such as after exposure to cold; conversely, a reduction in these effects results in vasodilatation.

The development of collateral circulation which results from stenosis or a major obstruction of the arteries influences the degree of ischaemia. Some collateral vessels are present in normal tissue, but do not dilate until arterial obstruction appears, while other capillaries develop in weeks or months. The adrenergic nerves, which are part of the autonomic nervous system, are responsible for vasoconstriction or dilatation of the collateral vessels in response to the increase in arterial pressure, with the result that the flow of blood to the tissue is improved. Substances produced by the endothelial cells which induce new blood vessel formation (neoangiogenesis) and vasodilatation were recently discovered. The production of VEGF (Vascular Endothelial Growth Factor), which seems to be responsible for the majority of the angiogenic and vasodilatory effect that results from stenosis or arterial obstruction, appears to be particularly important.

Experiments with isolated animal muscles have demonstrated that continuous electrical stimulation for 5 days (stimulation of 0.3 ms of amplitude, frequency of 150 Hz and voltage of 0.1 V) increases VEGF production, the number of capillaries and the

blood flow (Kanno S, Odam Abe M. Circulation 1999; 99, 2682-87).

Patients suffering from acute ischaemia or initial infarction have increased production of VEGF in the myocardium and in the endothelial cells of the capillaries and arterioles (Lee SH, Wolf PL, Escudero R, N Engl J. Med 2000, 342. 626-33).

The revascularisation induced by a transmyocardial laser with the aim of reducing angina pain is accompanied by an increase in VEGF and angiogenesis (Horvath, Chiu E, Maun AC, Annals of thoracic surgery 1999, 68. 825-29).

Modern technology offers some highly sophisticated instruments which allow the use of new techniques such as transmyocardial laser revascularisation, but these techniques are invasive and have limited effects.

The treatment of peripheral vascular disease is usually unsatisfactory. Vasodilators have a modest effect, and sympathectomy is ineffective. The treatment with VEGF produced by biotechnology is not without side effects. The only therapeutic solution is vascular surgery.

In practice, a really effective system for the treatment of peripheral vascular disorders has not been found yet. Vasodilators give poor results, treatment with VEGF based on recombinant DNA is not safe enough, and even surgery is just one of the various alternatives, which has not demonstrated any real efficacy.

Although the experiments described above seem to suggest that electrical stimulation of the muscles has beneficial effects on the circulation, the problem remains of excessive duration of the stimulation and of need to reach nerves or muscles with the stimulus. The present invention proposes an apparatus for the treatment of ischaemic disease which can generate and apply a series of pulses of which voltage and duration are controlled, suitable for stimulating the patient and eliciting an effective response, so as to eliminate inflammation from the part of the body treated, to activate the peripheral microcirculation and stimulate VEGF production.

The apparatus according to the invention uses a non-invasive

technique, because the stimulus is transmitted transcutaneously by means of electrodes.

The signals emitted by the machine are sent to the vascular receptors where they induce vasodilatation and stimulate VEGF release.

Using the apparatus according to the invention, ischaemia can be treated and ischaemic pain reduced.

The invention is based on a series of studies conducted by the applicants which demonstrate that by applying a series of electrical pulses to the patient, a biochemical response can be induced which not only can eliminate inflammation from the part of the body treated and reduces or eliminates pain, but also has a rapid muscle-relaxant effect, and stimulates vasodilatation and VEGF production.

However, an apparatus capable of also detect the response of the tissues to electrical stimulation and vary the stimulation parameters is needed to obtain the desired result.

For this purpose, the invention provides for an apparatus capable of generating electrical pulses whose variables can activate the patient's neurophysiological control systems.

The pulse parameters are defined on the basis of the bioreaction of the tissues. The intensity of the pulse is directly regulated by the patient.

After establishing experimentally that the apparatus according to the invention produces excellent results with muscle relaxation, the inventors formulated the hypothesis that the same apparatus might effectively induce vasodilatation and stimulate VEGF production.

Subsequent experiments demonstrated that this hypothesis was well-founded, and that the machine to which the invention relates produces the postulated results.

An embodiment of the machine is illustrated in the attached figures, in which:

- figure 1 is a block diagram of the apparatus according to the invention;
- figure 2 is the circuit diagram of the forward/back selector switch in the circuit shown in figure 1;

- figure 3 is the circuit diagram of the selector switch-counter logic network of the circuit shown in figure 1;
- figure 4 is a diagram of the up/down circuits, + DAC;
- figure 5 is the circuit diagram of the output stage of the circuit shown in figure 1;
- figure 6 is the circuit diagram of the timer in the circuit shown in figure 1;
- figure 7 is the circuit diagram of the automatic pulse train width regulator in the circuit shown in figure 1;
- figure 8 is the circuit diagram of the frequency regulator and timer in the circuit shown in figure 1;
- figure 9 is the circuit diagram of the control activated by the patient in the circuit shown in figure 1;
- figure 10 shows the concentration of VEGF versus time, after a treatment on patients affected by distal arterial obstruction (Example 2).

The circuits illustrated in the figures do not require a more detailed explanation because the information obtainable from the drawings is sufficient to allow an expert in the field to implement the invention.

The apparatus includes devices which can generate and regulate a series of electrical pulses that are sent to a pair of electrodes at the output, and is fitted with a control which allows the patient to regulate at least one of the control parameters of the said pulses, especially the voltage.

The electrodes, one active and one passive (or reference) electrode, are applied in different positions, depending on the tissue treated.

These regulations can be performed by means of an ordinary control fitted with pushbuttons and/or potentiometers which is activated by the patient.

The circuit shown in figure 2 allows forward/back regulation, in that it allows the patient to select an increased or reduced voltage, while the circuit shown in figure 3 is a counting circuit which counts the number of steps set with the control, in order to calculate the extent of the variation to be imparted to the output voltage signal.

In particular, the amount of this voltage variation is between 0.47 and 0.63 volts.

The digital count signal output from circuit 3 is then converted into an analog signal in the circuit shown in figure 4, where the pulse trains are generated that then pass to the output stage shown in figure 5 after being suitably regulated by the circuits shown in figures 6, 7 and 8.

The circuits shown in figures 6 and 7 regulate the duration (width) of the pulses and the increase in width between two successive pulse trains.

The circuit shown in figure 8 is the timer which determines the duration of the pulse train, while figure 9 shows the circuit diagram of the control activated by the patient.

During the initial stage of the experiments, the apparatus was regulated so as to generate a series of pulses of the square-wave type with a voltage of approx. 80 volts, the width of each pulse being selectable between 10 and 90 microseconds, and the frequency being selectable between 1 and 999 pulses a second.

The electrodes at the output of the apparatus were applied to the epidermis at the area to be treated and in particular one to the motor point and the other to the muscle belly.

The tests were performed by effecting treatments of different frequencies ranging from 1 to 420 pulses a second, and different widths, ranging from 10 to 50 microseconds, for a total time of 10 to 15 minutes.

120 patients suffering from orthopaedic disorders whose main component was local ischaemia or inflammation were treated.

The results demonstrated good vascularisation of the tissues, but there was no significant improvement in the inflammation.

The pulses were checked with an oscilloscope, which showed that the pulse in contact with the skin underwent considerable deformation, and the patient developed evident tolerance after only 3 minutes.

During a second series of tests, the machine was set to vary the width of the pulses after each series of pulses applied in

the same cycle, in order to prevent tolerance by the patient and deformation of the pulses.

300 patients suffering from orthopaedic pathologies complicated by inflammation and ischaemia were treated by applying several series of pulses and increasing the pulse width from time to time during the same treatment.

The results demonstrated that reduction of inflammation and improvement in blood flow were associated with modulation of the neurovegetative nervous system.

A further test was then conducted with 120 patients suffering from orthopaedic pathologies associated with phlogosis or deficiency of the local microcirculation.

The treatment comprised 12 ten-minute sessions in which electrodes were applied to the epidermis at a distance of approx. 10-15 centimetres apart.

The patient had the possibility to increase or decrease the voltage of the pulse during stimulation with a remote control.

The variation in intensity of the pulse voluntarily decided on by the patient and the variation in the physiological bioreaction time or muscle relaxation times were observed simultaneously with a double-trace oscilloscope.

These first tests confirmed the inventor's intuition, namely that the application of series of electrical pulses under given voltage, frequency and width conditions could produce the desired results.

The following examples and tables show the results of further, more detailed tests.

Example 1

Muscle relaxation (Tables 1a/d - 2)

With the machine according to the invention, one electrode was applied to the motor point and one to the belly of the trapezius muscle, and pulse trains were sent to the patient for 30 seconds at a voltage of approx. 180 volts, with a frequency of one pulse a second and a width of 10 microseconds.

During the second phase, lasting 5 seconds, the pulses were applied at the frequency of one a second, with a width of 20 microseconds.

As the test continued, the parameters were varied from time to time as indicated in the annexed tables 1a to 1d until the muscle reached spasm, then relaxed and remained in that condition.

As will be seen from the graph in table 2, after approx. 12 phases of treatment the muscle reached an almost permanent state of relaxation.

This relaxation corresponds to the maximum degree of vascularisation and the maximum anti-flogistic effect.

The anti-inflammatory treatment programme is shown in table 3 and the associated graph 4.

Table 5 and the associated graph 6 show a treatment programme for activation of the microcirculation.

From above it appears that the apparatus according to the invention is able to relax the muscles, induce vasodilatation, increase the blood flow and stimulate new vessel production.

The technique is non-invasive because the signal is transmitted transcutaneously through electrodes.

The signals emitted with this new technology are conducted by the sensory and proprioceptive fibres of the autonomic nervous system, and reach the vascular and muscle receptors through which vasodilatation and muscle relaxation is produced, the blood flow is increased and VEGF release is stimulated.

The treatment combats ischaemia and reduces pain. The clinical symptoms of ischaemia, such as claudication due to contraction of the calf, thigh or buttocks and pain at rest, rapidly regress, and the patient walks normally.

Vasodilatation and increased blood flow take place in all parts of the body to which the treatment is applied. The effect is long-lasting, however, its duration depends on the degree of arterial obstruction and the time taken for collateral circulation to develop. Measurements taken with a laser doppler demonstrate significant increases in blood flow in the treated areas.

The efficacy of the treatment is demonstrated by the following example.

Example 2

12 patients with distal arterial occlusion (7 with occlusion of the tibial artery and 5 with occlusion of the femoral artery) were studied before, during and after stimulation with the new technology.

The VEGF (pg/ml) was assayed at the times shown in figure 10.

As can be seen, an increase in VEGF was already evident 2-3 minutes after the start of the stimulus, it peaked after 5 mins (the increase was approx. 50%), and returned to normal after 15 mins. These data demonstrate for the first time that the application of the invention is able to increase VEGF, the most potent specific endogenous angiogenic factor identified to date. Increased VEGF production was also accompanied by vasodilatation. By contrast with what happens in laboratory animals subjected to a direct stimulus on the isolated muscle and nerve, this method enables the stimulus to be induced through the skin with electrodes. The time taken to stimulate VEGF is a few minutes, whereas the electrical stimulation used in animals takes days to achieve the same result. In the case of severe stenosis or arterial obstruction, recurrence of the ischaemia symptoms after suspension of the treatment is often due to a deficiency in the development of collateral circulation. In this case the treatment must be continued or an arterial bypass performed, which may be followed by new treatment to ensure complete healing of the tissues.

Maintenance of a high blood flow in the treated tissues increases the trophism of the tissue, prevents necrosis and heals ulcers.

The application of this invention to specific parts of the body rather than directly to the heart induces coronary vasodilatation and increases VEGF production in the coronary sinus.

This effect has been observed in 3 patients who underwent cardiac catheterisation, from whom blood samples were taken at the same time to assay the cardiac VEGF.

The treatment can also be applied to lesions of the spinal column and pain syndromes of the back and neck.

The spinal column, together with the spinal cord, nerve roots, spinal ligaments and paraspinal muscles are the sites of some of the most frequent disorders to which human beings are liable. The cervical and lumbar pain which originates in these structures affects nearly everyone sooner or later. This disorder, together with alcoholism, is one of the major causes of absenteeism.

The most important symptom of lesions of the spinal column and the various structures that compose it is pain, which may be local or muscle-related. Pain is caused by irritation of the nerve ending at the site of the pathological process. Treatment of patients with cervical and back pain is very difficult, and often ineffective. Rest, combined with analgesics, is currently considered to be the best treatment. Physiotherapy is performed with the aim of strengthening the paravertebral muscles to prevent painful relapses. Neck manipulation is potentially dangerous. This invention provides an innovative approach to the treatment of lesions of the spinal column.

As mentioned, this new technology acts through the autonomic nervous system, targeting the structures of the spinal column which are most often affected by painful disorders, such as the ligaments, periosteum and paravertebral muscles, by acting on the muscle spindles, the Golgi tendon organs and the joint proprioceptors. Its action is followed by a reduction in oedema, inflammation and pain.

This treatment has been tested on some 200 patients suffering from cervical or lumbar pain.

Most of the patients felt better within a few days (3-10). 60 of them had a slipped disc and 10 of them had already been operated on for slipped disc but still felt pain. The treatment was effective in 92% of cases. 90% of the patients suffering from slipped disc did not need an operation because the compression or inflammation symptoms of the nerve root were eliminated by the treatment.

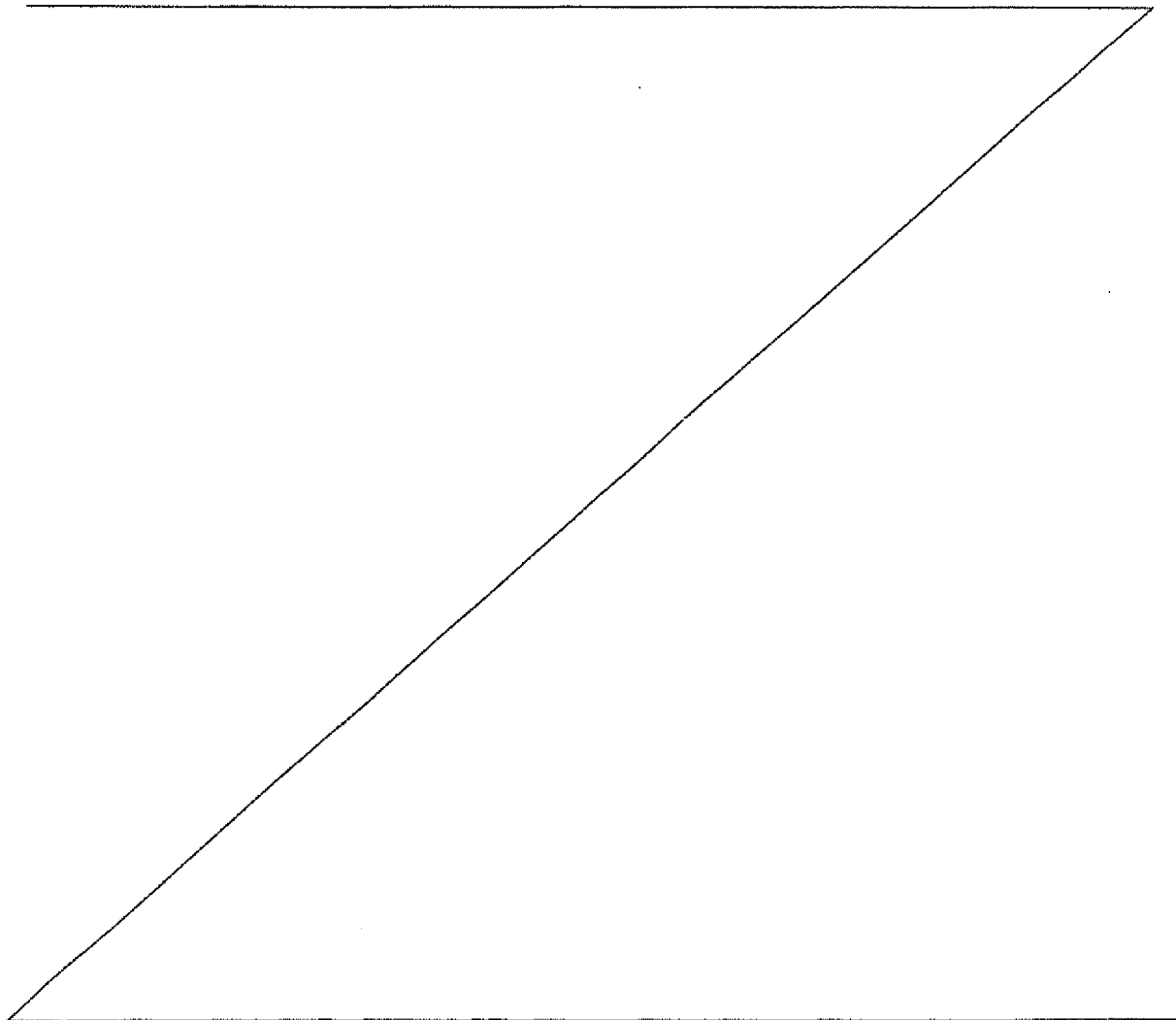
The results obtained with this method demonstrate that this technique has multiple effects on mechanical lesions of the spinal column and their complications:

- it eliminates pain and returns the proprioceptive sensitivity to normal;
- it restores normal muscle contractility;
- it increase the blod flow;
- it eliminates inflammation.

The same technology has been tested in other pathologies.

For example, the invention has been successfully tested in the treatment of numerous other disorders such as in particular cervical, back, hip, thigh and knee pain, knee instability, Achilles tendinitis, calcaneal spur, metatarsalgia, and shoulder, elbow, wrist and hand pathologies.

In conclusion, this new treatment improves the quality of life and reduces one of the most frequent clauses of absenteeism.



CLAIMS

- 1) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders characterized in that it comprises:
 - means for generating frequencies of electrical pulses;
 - means for applying said pulses to a patient through the epidermis;
 - means for evaluating the tissue reaction;
 - means for varying said pulses on the basis of the tissue reaction detected;at least one of said means being controllable by the patient/user.
- 2) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to claim 1, characterized in that it comprises means suitable for enabling the patient to control the voltage of the applied pulses.
- 3) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to claim 1 or 2, characterised in that it includes a pair of electrodes designed to transmit the said pulses, one of which can be applied to the motor point and the other to the muscle belly in the area to be treated.
- 4) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to each one of the preceding claims, characterised in that said means suitable for transmitting said pulses include devices able to vary the voltage, amplitude and frequency of the said pulses.
- 5) Apparatus according to each of the claims 1 to 4, characterised in that it includes means suitable for regulating the amplitude and frequency of the pulses, said means being activated directly by the patient.
- 6) Apparatus for the treatment of muscle contraction according to claim 1, characterised in that it includes a pair of electrodes designed to transmit said pulses, one of which can be applied to the motor point and the other to the muscle belly in the area to be treated.
- 7) Apparatus for anti-inflammatory treatments according to claim 1, characterised in that it includes an active

electrode designed to be applied at the site of inflammation, and a passive electrode external to the said site.

- 8) Apparatus for the treatment of vascular disorders according to claim 1, characterised in that it includes an active electrode designed to be applied upstream of the occlusion and a passive electrode designed to be applied downstream thereof.
- 9) Apparatus for the activation of the microcirculation according to claim 1, characterised in that it includes an active electrode designed to be applied at the ischaemic site and a passive electrode designed to be applied close to the venous plexus.
- 10) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to claim 1, characterised in that it includes means suitable for varying the voltage of the pulses applied, with variable increments between 0,47 V and 0,63 V for each step of the up/down circuit.
- 11) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to claim 1, characterised in that it includes means suitable for varying the number of pulses applied between 1 and 420 per second.
- 12) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to claim 11, characterised in that it includes means suitable for varying the width of the pulses between 10 and 50 msec.
- 13) Apparatus for the treatment of vascular and/or muscle and/or tendon disorders according to the description and drawings.

Milan, 28th July 2000.

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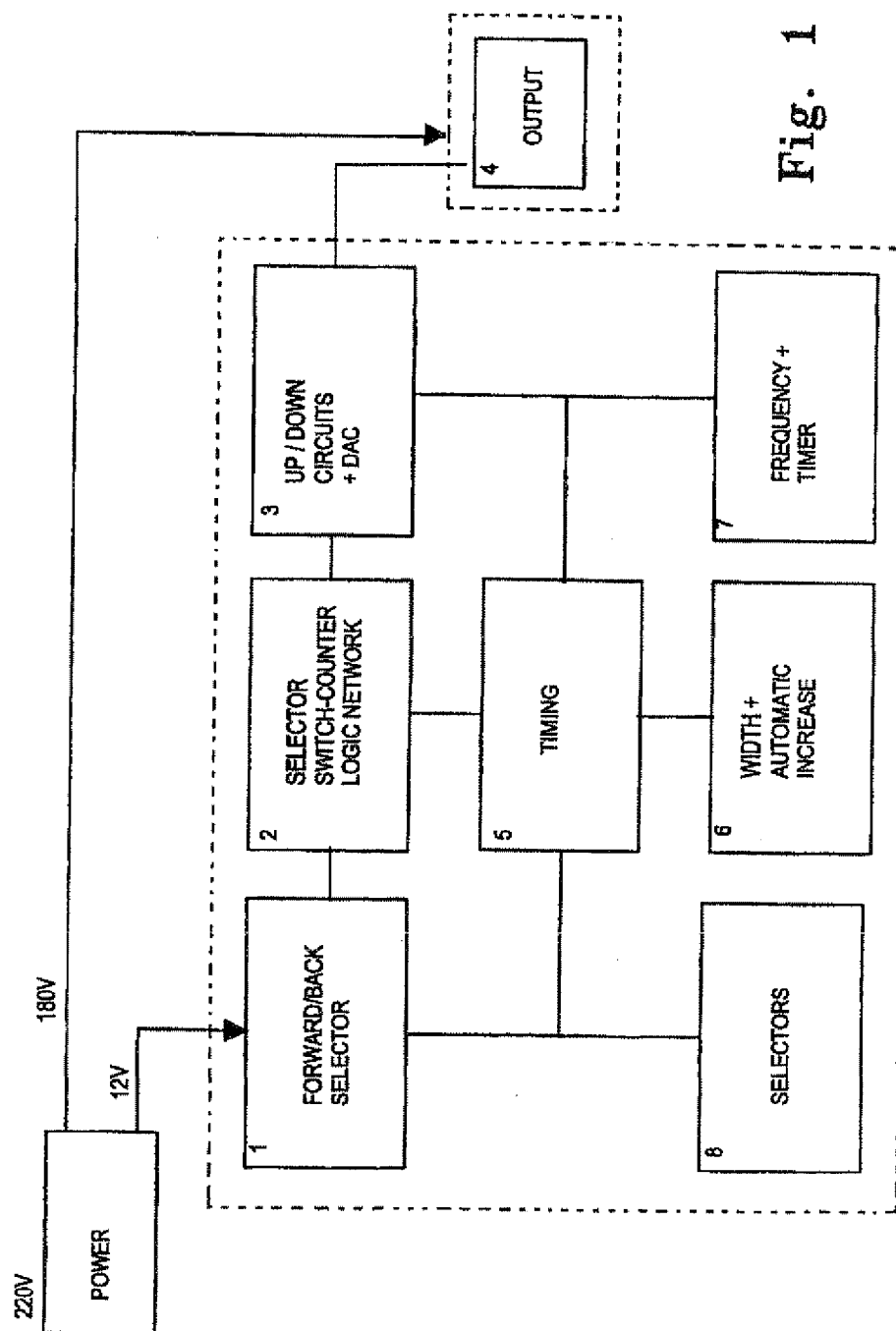


Fig. 1

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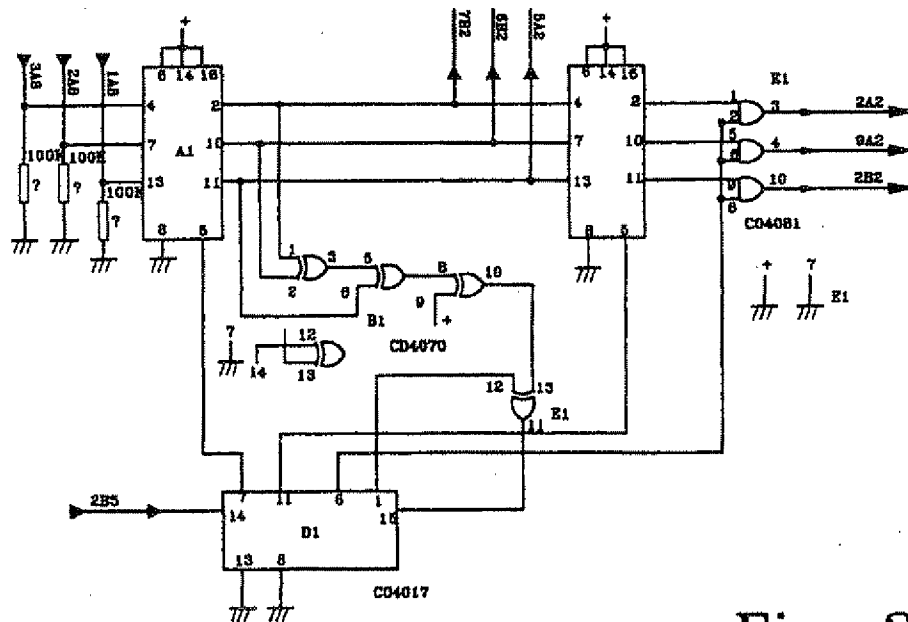


Fig. 2

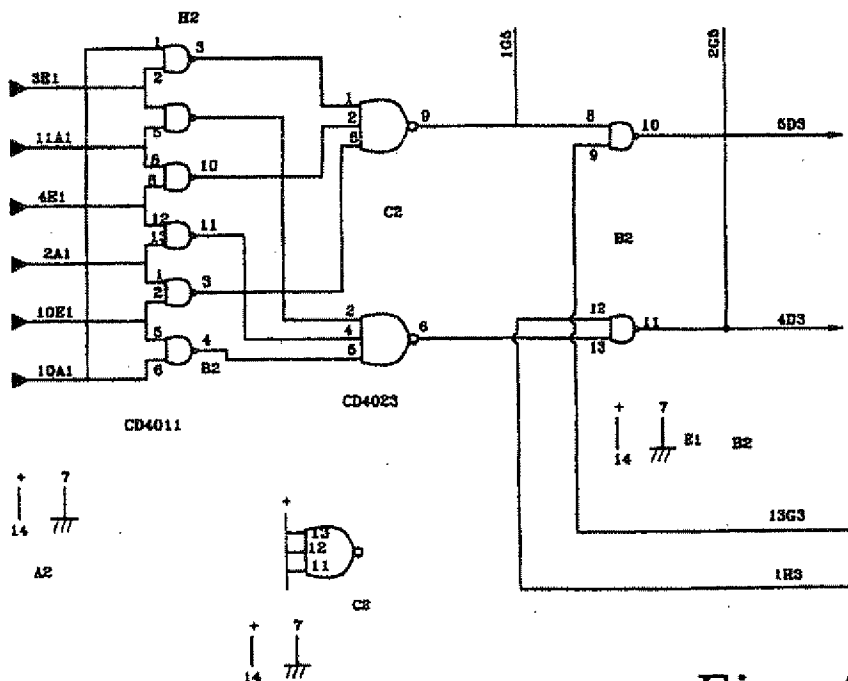


Fig. 3

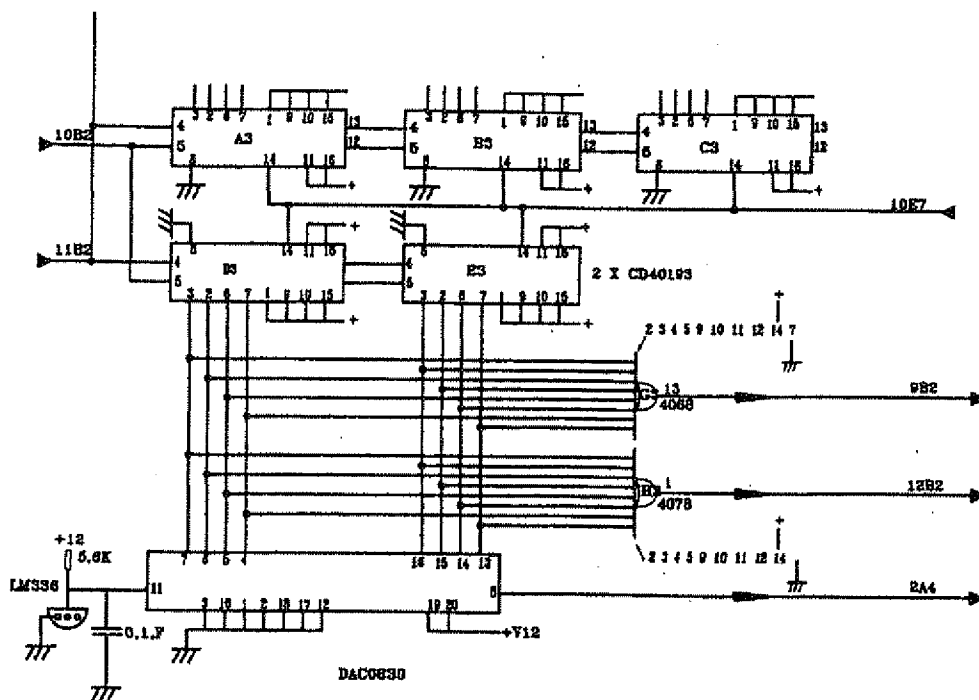


Fig. 4

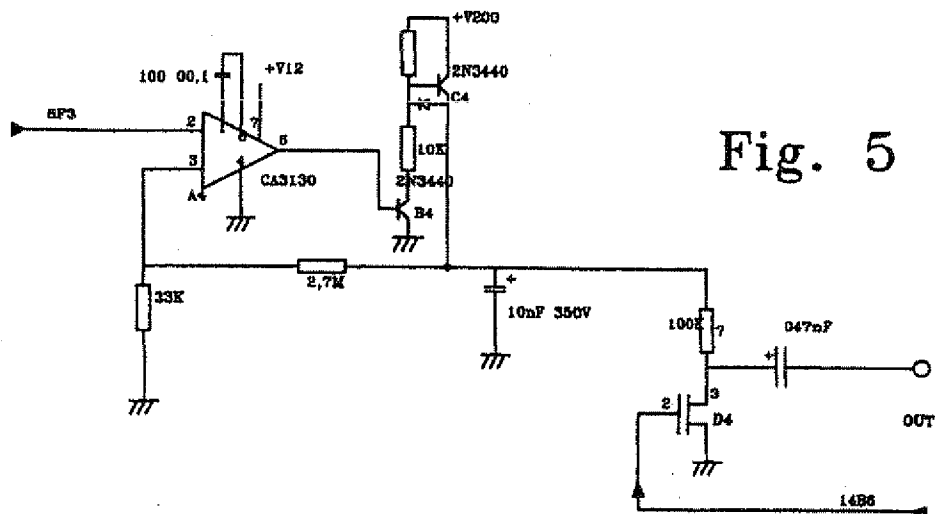


Fig. 5

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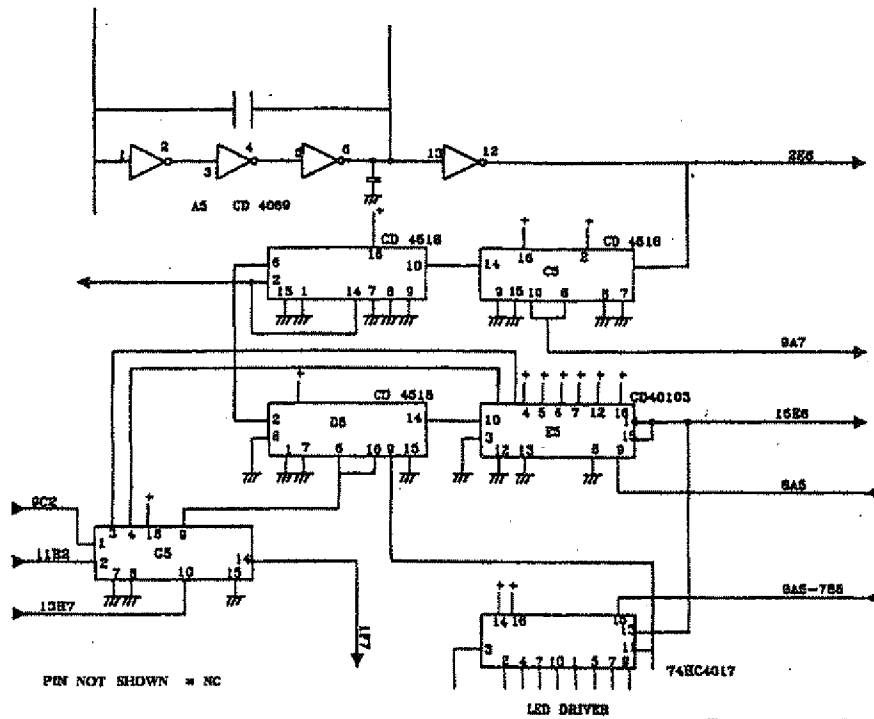


Fig. 6

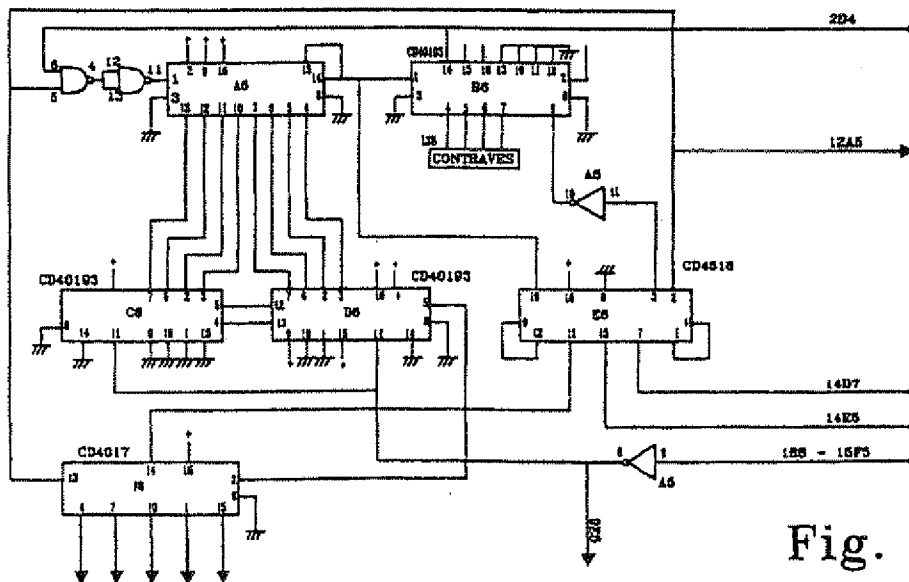
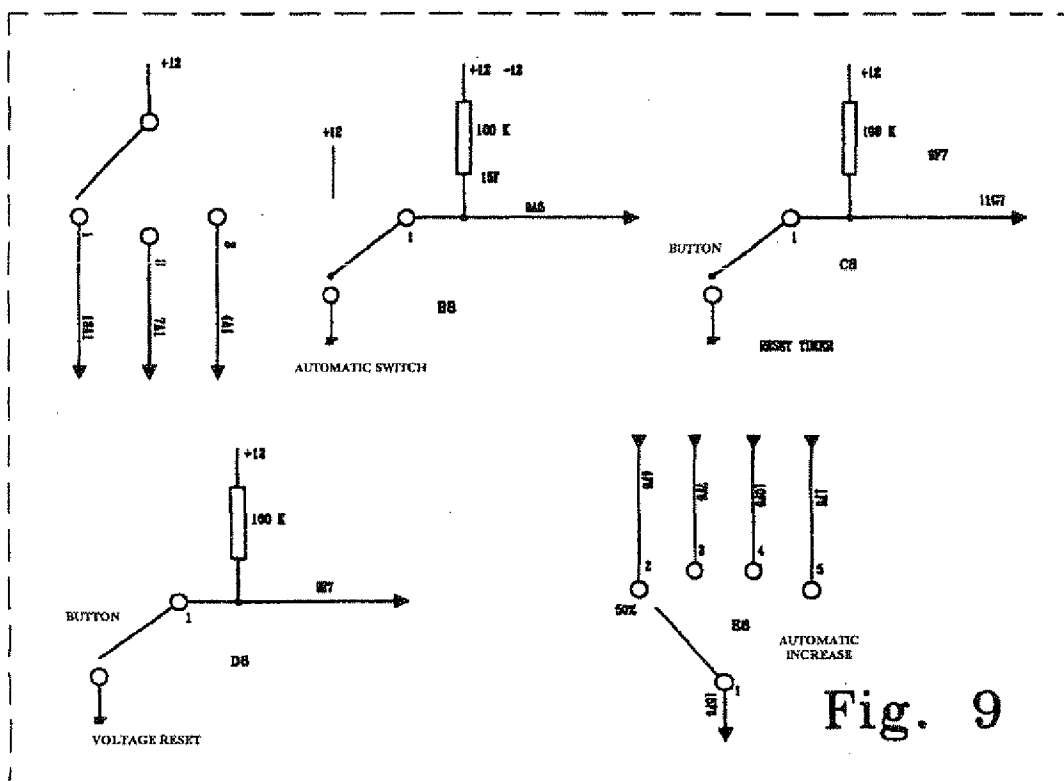
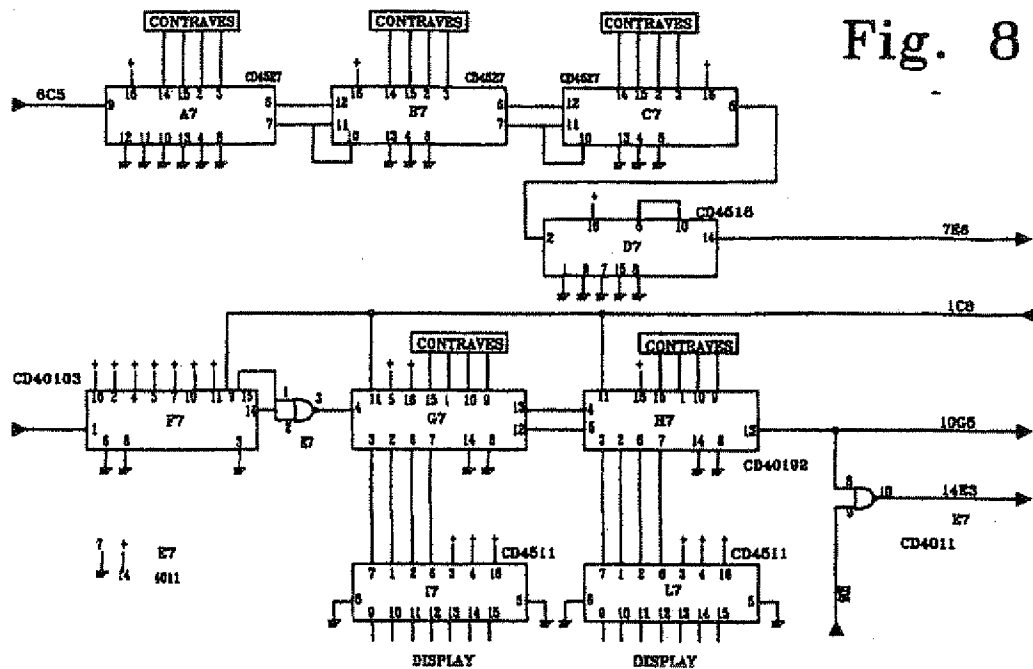


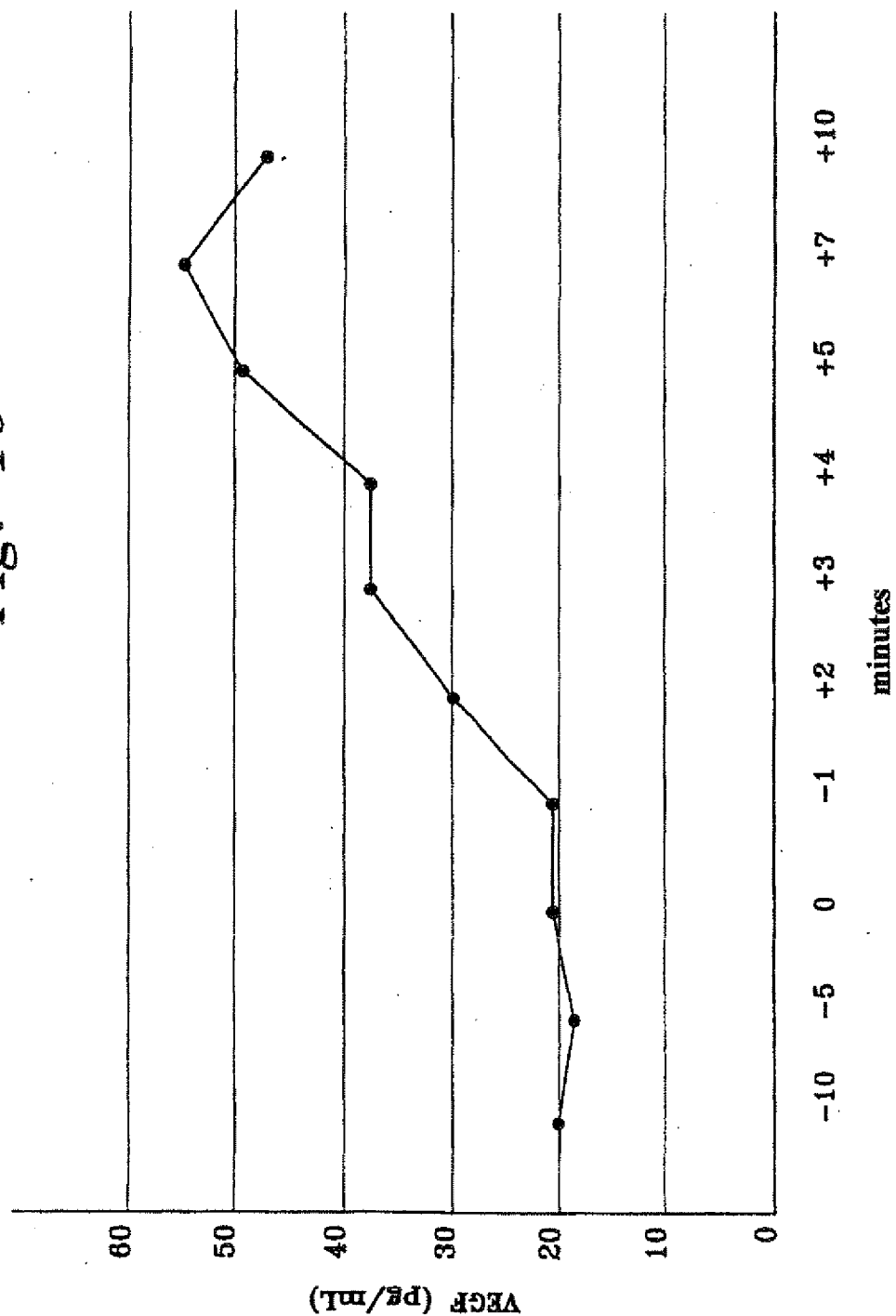
Fig. 7

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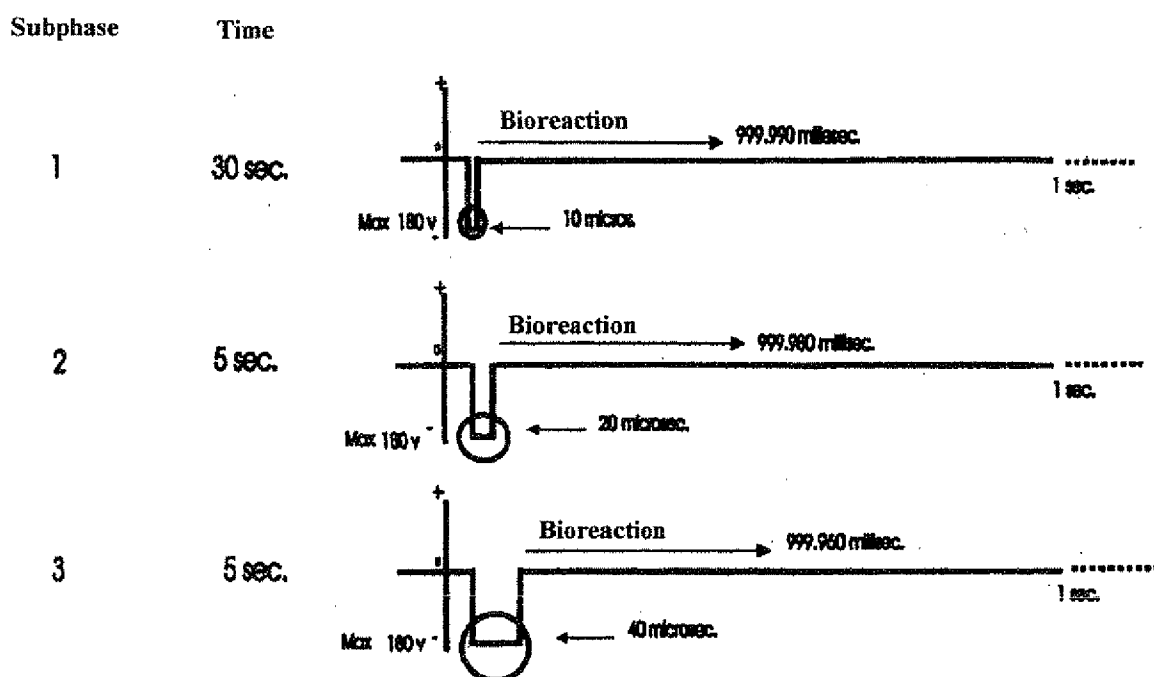
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Fig. 10



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Subphase	Time/sec.	Frequency	Width/microsec.	Bioreaction/millsec.
1	30	1	10	999,990
2	5	1	20	999,980
3	5	1	40	999,960



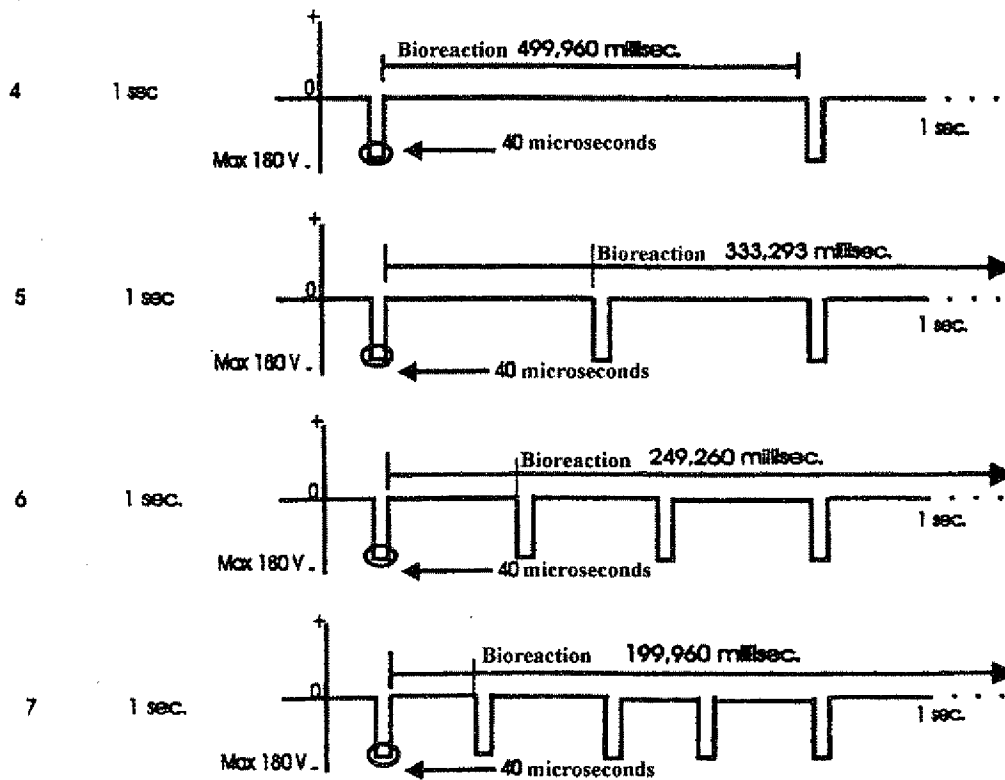
Tab. 1a

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Tab. 1b

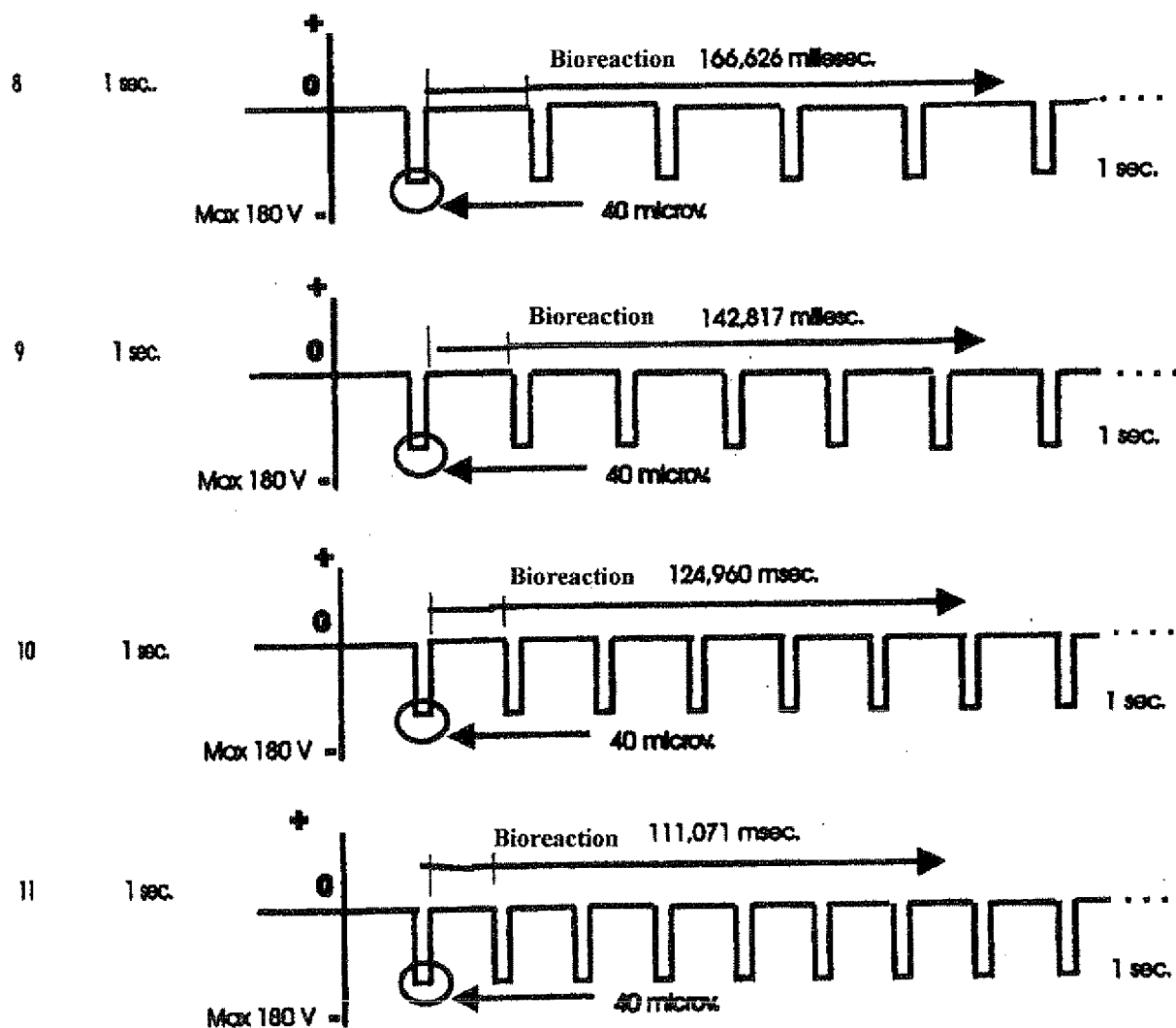
Subphase	Time//sec.	Frequency	Width/microsec.	Bioreaction/millisec.
4	1	2	40	499,960
5	1	3	40	333,293
5	1	4	40	249,260
7	1	5	40	199,960
8	1	6	40	166,626
9	1	7	40	142,817
10	1	8	40	124,960
11	1	9	40	111,071

Subphase Time



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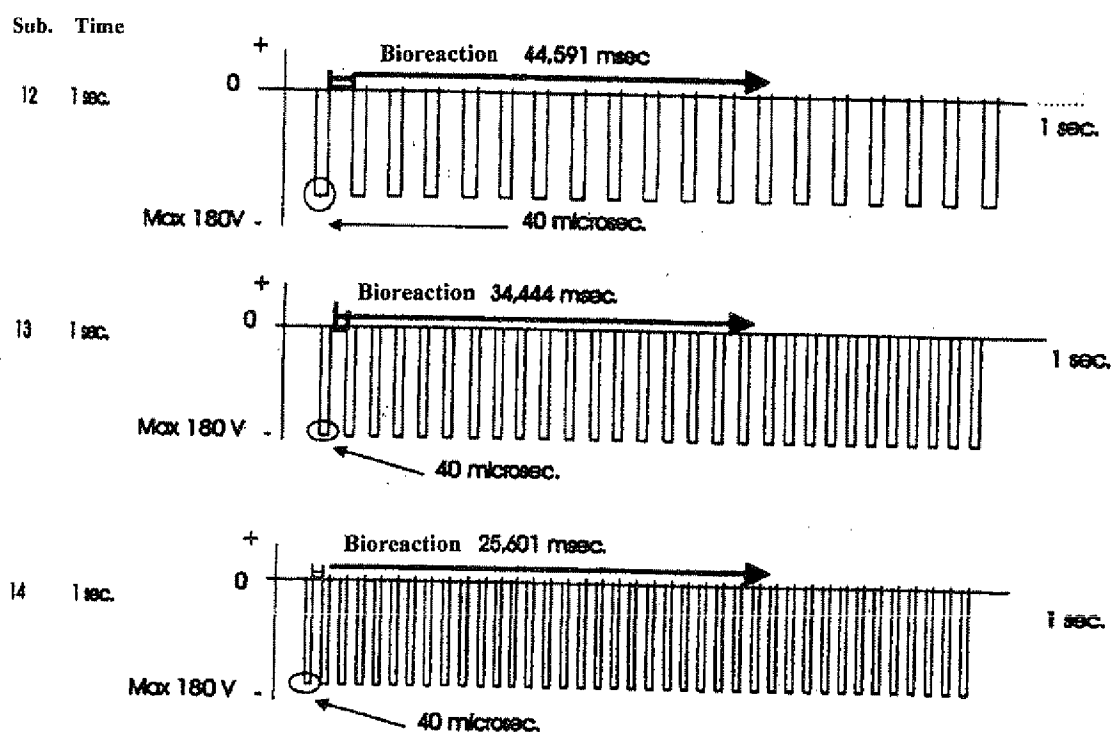
Subphase Time



Tab. 1c

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Subphase	Time/sec.	Frequency	Width/microsec.	Bioreaction/msec.
12	1	19	40	44,591
13	1	29	40	34,444
14	1	39	40	25,601

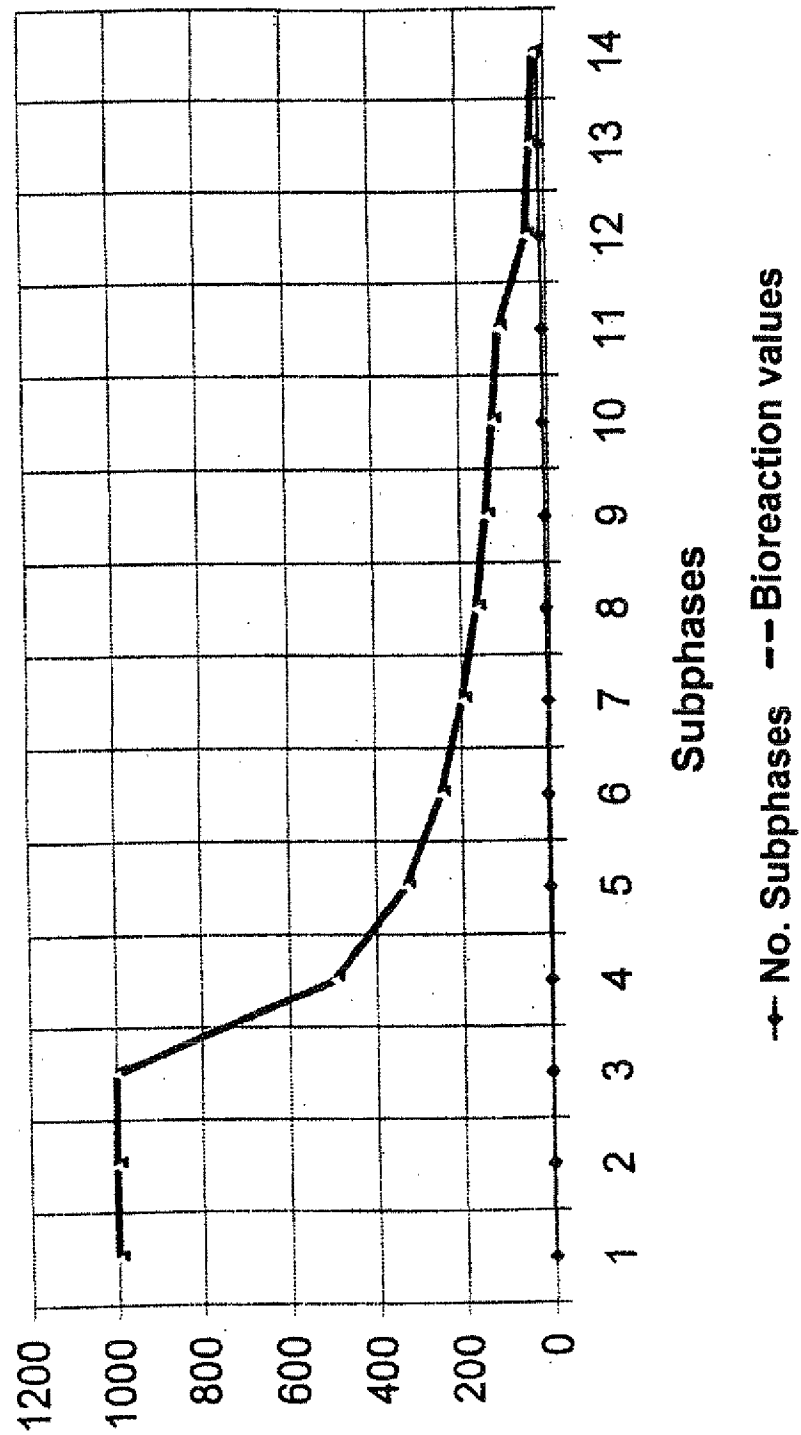


Tab. 1d

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Tab. 2

Bioreaction A.S.M. Graph



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Tab. 3

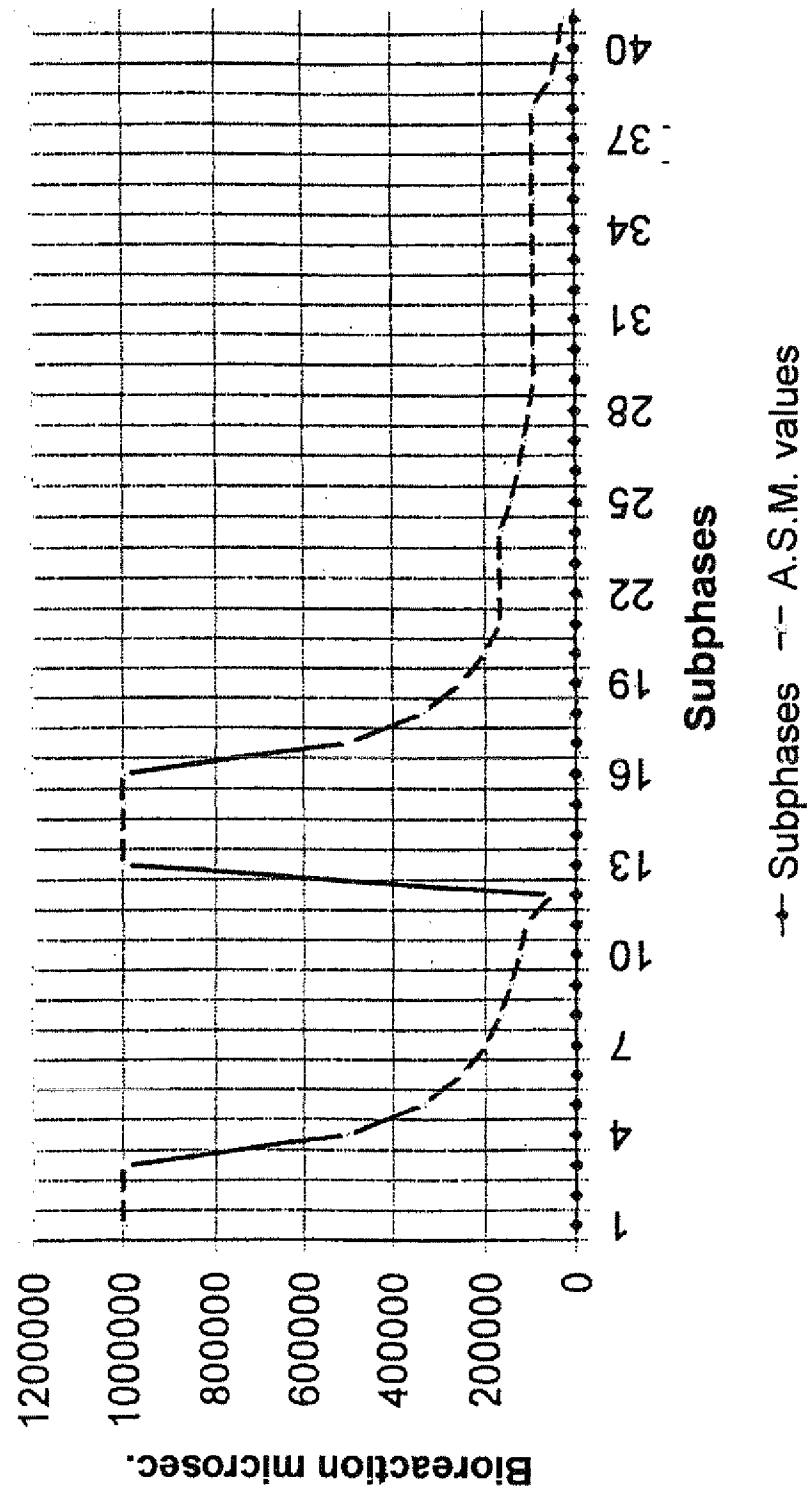
Anti-inflammatory treatment program

Subphases	Time/sec.	Frequency	Width/mic.	Bioreaction/microsec.
1	30	1	10	999.990
2	5	1	20	999.980
3	5	1	40	999.960
4	1	2	40	499.960
5	1	3	40	333.293
6	1	4	40	249.960
7	1	5	40	199.960
8	1	6	40	166.627
9	1	7	40	142.817
10	1	8	40	124.960
11	1	9	40	111.071
12	1	19	40	52.592
13	8	1	10	999.990
14	4	1	20	999.980
15	2	1	30	999.970
16	1	1	40	999.960
17	8	2	40	499.960
18	4	3	40	333.293
19	2	4	40	249.960
20	1	5	40	199.960
21	8	6	10	166.657
22	4	6	20	166.647
23	2	6	30	166.637
24	1	6	40	166.627
25	8	7	40	142.817
26	4	8	40	124.960
27	2	9	40	111.071
28	1	10	40	99.960
29	4	11	20	90.889
30	4	11	40	90.869
31	4	11	20	90.889
32	4	11	40	90.889
33	4	11	20	90.889
34	4	11	40	90.869
35	4	11	20	90.889
36	4	11	40	90.869
37	4	11	20	90.889
38	4	11	40	90.869
39	1	21	40	47.579
40	1	31	40	32.218
41	1	41	40	24.350

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Tab. 4

Bioreaction A.S.M. Graph



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Program of microcirculation activating treatment

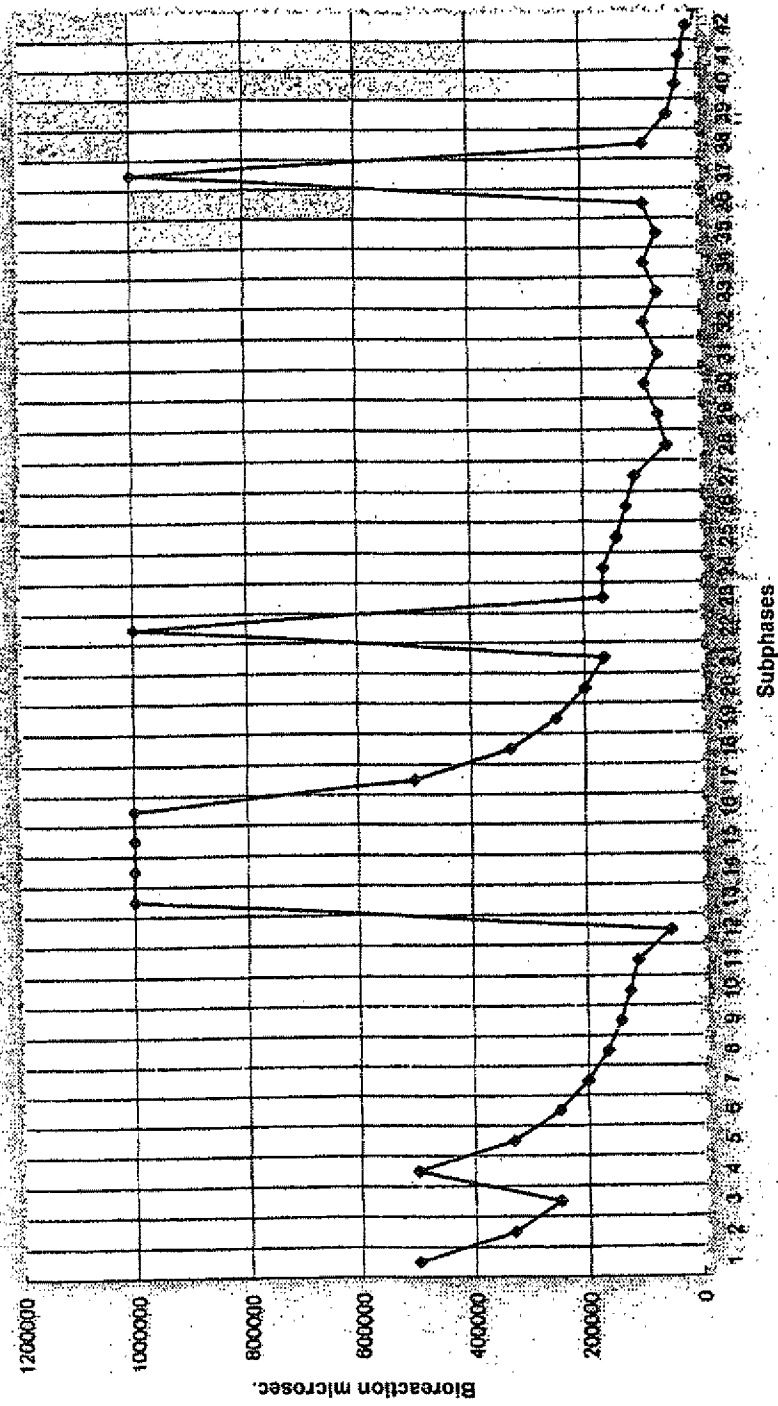
Tab. 5

Subphases	Time/sec.	Frequency	Width/microsec.	Bioreaction/microsec.
1	30	2	10	499.990
2	5	3	20	333.313
3	5	4	40	249.960
4	1	2	40	499.960
5	1	3	40	333.293
6	1	4	40	249.960
7	1	5	40	199.960
8	1	6	40	166.627
9	1	7	40	142.817
10	1	8	40	124.960
11	1	9	40	111.071
12	1	19	40	52.592
13	8	1	10	999.990
14	4	1	20	999.980
15	2	1	30	999.970
16	1	1	40	999.960
17	8	2	40	499.960
18	4	3	40	333.293
19	2	4	40	249.960
20	1	5	40	199.960
21	8	6	10	166.657
22	4	1	20	999.980
23	2	6	30	166.637
24	1	6	40	166.627
25	8	7	40	142.817
26	4	8	40	124.960
27	2	9	40	111.071
28	1	19	40	52.592
29	4	15	10	66.657
30	4	11	40	90.869
31	4	15	20	66.647
32	4	11	40	90.869
33	4	15	10	66.657
34	4	11	40	90.869
35	4	15	10	66.657
36	4	11	40	90.869
37	4	1	10	999.990
38	4	11	40	90.869
39	1	21	40	47.579
40	1	31	40	32.218
41	1	41	40	24.350
42	1	81	40	12.306

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Tab. 6

Bioriaction A.S.M. graph



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